REMARKS/ARGUMENTS:

Claims 1, 6, 14, 20, 25, 30, 34, 36-38, 40, and 43-45 are amended. New claims 46-48 are added. Support for the amendments and the new claims can be found throughout the specification and in particular at page 3, lines 14-21 and page 8, line 10 – page 9, line 2, and page 16, lines 3-7 of the specification. No new matter is introduced.

Claims 1-48 are pending in this application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

Rejoinder of Product and Process Claims:

MPEP § 821.04 provides for a rejoinder procedure when applicant elects claims directed to the product, and a product claim is subsequently found allowable. In particular, MPEP § 821.04 allows rejoinder of withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim. Accordingly, if the Examiner finds product claims 1, 36, 37, 38, 40, 46, or 47 allowable, applicants respectfully request rejoinder of process claims 6-35, which depend from the product claims, with the allowed product claims. In preparation for rejoinder, the withdrawn process claims have been amended to conform to the scope of the potentially allowed product claims.

Claim Rejections Under 35 U.S.C. § 102:

The Examiner maintained the rejection of claims 1-5 under 35 U.S.C. § 102(b) as being anticipated by Goldberg GI (WO 98/12309; "Goldberg"). (Office Action, §5) The Examiner also noted that claims 37-41 and 43-45 were newly rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite for having a narrow limitation followed by a broad limitation, and that if these claims were amended to read on "comprising" language, the same rejection could be applied.

Applicants respectfully assert that claims 1-5 are not anticipated by Goldberg because Goldberg does not disclose the claimed peptides (see the Amendment filed September 7, 2004). However, for the sole purpose of moving this application forward, Applicants have amended claim 1 such that it is now directed to anti-angiogenic peptide comprising a sequence of SEQ ID NO:2. Because Goldberg does not teach the sequence of SEQ ID NO:2, Goldberg does not anticipate amended claim 1, nor does it anticipates claims 3-5 which depend from claim 1. None of claims 37-41 and 43-45 has been amended to recite "comprising." Thus, these claims are not subject to the instant rejection and withdrawal of the rejection is respectfully requested.

The Examiner further maintained the rejection of claims 1-5 under 35 U.S.C. § 102(b) as being anticipated by Brooks *et al.* (WO 97/45137; "Brooks"). (Office Action, §6) The Examiner also noted that claims 37-41 and 43-45 were newly rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite for having a narrow limitation followed by a broad limitation, and that if these claims were amended to read on "comprising" language, the same rejection could be applied. Applicants disagree.

Claims 1 and 3-5 are not anticipated by Brooks because Brooks does not disclose the claimed peptides (see the Amendment filed September 7, 2004). However, for the purpose of moving this application forward, Applicants have amended claim 1 such that it is now directed to an anti-angiogenic peptide comprising a sequence of SEQ ID NO:2. Since Brooks does not teach the sequence of SEQ ID NO:2, it does not anticipate amended claim 1. Brooks also does not anticipate claims 3-5, which depend from claim 1. None of claims 37-41 and 43-45 has been amended to recite "comprising." Thus, these claims are not subject to the instant rejection. Withdrawal of the rejection is respectfully requested.

NEW REJECTIONS

Claim Rejections Under 35 U.S.C. § 112, second paragraph:

The Examiner rejected claims 37-41 and 43-45 under 35 U.S.C. § 112, second paragraph, as being indefinite. (Office Action, §§ 8-9)

Applicants disagree. Claims 37-41 and 43-45 are not indefinite because they particularly point out and distinctly claim the peptides of the invention. However, for the sole purpose of moving this application forward, Applicants have amended claims 37-38, 40, and 43-45 to clarify that the claims are directed to peptides consisting of composite sequences. In particular, it has been clarified that the closed transition "consisting of" refers to a combination of SEQ ID NO:1 and one flanking amino acid at the N-terminus, C-terminus, or both termini. For example, amended claim 37 reads as:

> A peptide consisting of a combination of SEQ ID NO:1 and one additional flanking amino acid at the N-terminus of SEQ ID NO:1.

This claim is drawn to a peptide consisting of a composite sequence. The composite sequence has two parts: a flanking amino acid at the N-terminus, and the sequence of SEQ ID NO:1 following the flanking amino acid. As such, claims 37-41 and 43-45 unambiguously set forth the metes and bounds of the invention. Therefore, the rejection should be withdrawn.

Claim Rejections Under 35 U.S.C. § 112, first paragraph:

The Examiner further rejected claims 1-5, 37-41, and 43-45 under 35 U.S.C. § 112, first paragraph, for lack of enablement. (Office Action, §10)

With respect to claim 2, the rejection is moot due to the cancellation of the claim. With respect to the claims 1, 3-5, 37-41, and 43-45, Applicants disagree because the specification provides full support for these claims. However, for the sole purpose of moving this application forward, Applicants have deleted the term

"biologically equivalent" from claim 1. The rejection is thus moot with regard to amended claim 1, as well as claims 3-5, which depend from claim 1.

Applicants assert that the specification provides enablement for the peptides of claims 37-41 and 43-45. These claims are drawn to peptides consisting of composite sequences. Each composite sequence has two or three parts: the sequence of SEQ ID NO:1 or 2 with a flanking amino acid at the N-terminus, C-terminus, or both termini of either SEQ ID NO:1 or 2. The specification provides sufficient information which enables one skilled in the art to make and use these peptides.

It is generally well known in the art that amino acids can be added at the N-terminus, C-terminus, or both termini of a peptide without substantially altering the biological function of the peptide. For example, Kato et al. (1996, Plant Cell 8: 1601-1611, a copy of which is attached hereto as Exhibit A), demonstrated that a protein can be fused to the C-terminus of a peptide, which facilitates localization of the protein to a particular compartment of a cell, while preserving the biological function of the peptide (Table 1 on page 1607). Also, in the second example of U.S. Patent No. 6,780,843, a copy of which is attached hereto as Exhibit B, it is shown that a protein can be added to the N-terminus of a translocation peptide while preserving the biological function of the translocation peptide. Furthermore, the anti-FLAG M2 antibody described by Shelness et al. (1994, J. Biol. Chem. 269(12): 9310-9318, a copy of which is attached hereto as Exhibit C), recognizes an epitope peptide regardless of additional amino acid sequences at both the N-terminus and the C-terminus of the peptide). Because multiple amino acids can be added to the N-terminus, C-terminus, or both termini while preserving the biological functions of the peptides, it is reasonable to expect that the addition of merely a single amino acid to the N-terminus, C-terminus, or both termini of SEQ ID NO:1 or 2 will not substantially disturb the biological function of SEQ ID NO:1 or 2.

Furthermore, the specification expressly teaches that SEQ ID NO:1 "may be flanked by other amino acids" and provides an example of a peptide consisting of SEQ ID NO:1 and an additional flanking amino acid at each of the N- and C-termini

of SEQ ID NO:1, i.e., the peptide of SEQ ID NO:2 (page 3, lines 17-21). SEQ ID NO:1 is a peptide of 9 amino acids. SEQ ID NO:2 has a cysteine added at both the N-terminus and the C-terminus of SEQ ID NO:1, and has been shown to inhibit angiogenesis (page 27, line 2 – page 29, line 15 of the specification). Based on these teachings, those skilled in the art would have realized that, instead of cysteine, other single amino acids may be added to one or both termini of SEQ ID NO:1. Similarly, those skilled in the art would have understood that SEQ ID NO:2, which inhibits angiogenesis, may be further extended by an additional amino acid at one or both of its termini while maintaining an anti-angiogenic activity.

Additionally, as pointed out in the instant specification, it is well known in the art that certain amino acids can be substituted for other amino acids in a given peptide without any appreciable loss of function, and that in making such changes, substitutions of like amino acid residues can be made on the basis of relative similarity of side-chain substituents, for example, their size, charge, hydrophobicity, hydrophilicity, and the like (page 8, lines 10-15). The hydrophilicity values and the hydropathic index values assigned to the amino acids are provided in the specification. In particular, it is pointed out that an amino acid residue in a peptide can be substituted for another having a similar hydrophilicity value (e.g., within a value of plus or minus 2.0) or a similar hydropathic index value (e.g., within a value of plus or minus 2.0) without any appreciable loss of function of the peptide. See page 8, line 10 – page 9, line 2 of the specification. Given such guidance, one skilled in the art would expect to be able to substitute the cysteine having hydrophilicity value -1.0 and a hydropathic index of +2.5 with another residue at the N-terminus or the C-terminus of SEQ ID NO:2 with a similar hydrophilicity or a hydropathic index value and retain anti-angiogenic activity

Moreover, the specification fully satisfies the enablement requirement even if addition of some amino acids may substantially disturb the biological function of SEQ ID NO:1 or 2 because "[t]he law does not require a specification to be a blueprint in order to satisfy the enablement requirement" (*Staehelin v. Secher*, 24

U.S.P.Q. 2d 1513, 1516 (Bd. Pat. App. & Int. 1992)). Even in the relatively "unpredictable" arts, one need not necessarily disclose how to make each and every embodiment encompassed by the claim. For example, in *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976), the court noted that some experimentation is often to be expected in unpredictable areas of technologies. The court further observed that, if § 112 required a disclosure of a test with every species covered by a claim in an unpredictable art, then a prohibited number of actual experiments would have to be performed, discouraging the filing of patent applications in unpredictable areas. *Id.* The specification teaches how to determine which amino acids can be added to the N-terminus, C-terminus, or both termini of SEQ ID NO:1 or 2. For example, a CAM assay, a rabbit eye assay, or a chimeric mouse assay can be used to determine whether a peptide is capable of modulating angiogenesis in a tissue. See page 12, line 12 – page 6, line 14 of the specification. Using such methods, one skilled in the art would be able to identify the anti-angiogenesis peptides within the scope of the claimed invention.

Therefore, sufficient guidance and specific examples are given in the specification with respect to making the peptides of the invention. Merely routine experimentation, if any, would be required. The specification also teaches the use of these peptides, e.g., in formulating therapeutic compositions, inhibiting angiogenesis, treating diseases, detecting angiogenesis, and the like. See page 14, line 7 - page 26, line 28 of the specification. Accordingly, one skilled in the art would be able to practice the claimed invention without undue experimentation. Applicants submit that claims 37-41 and 43-45 are enabled by the specification in their full scope and that the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

NEW CLAIMS 46-48

New claims 46-47 are directed to anti-angiogenic peptides comprising the sequence of amino acids 1-10 or 2-11 of SEQ ID NO:2, i.e., the sequence of SEQ ID NO:1 with a cysteine added either to the N-terminus or the C-terminus of SEQ ID

NO:1. These peptides are not anticipated by Goldberg or Brooks because neither of the prior art references discloses the sequence of amino acids 1-10 or 2-11 of SEQ ID NO:2. Claims 46-47 are also fully enabled for the reasons set forth above. Therefore, Applicants respectfully request that claims 46-47 be allowed. Support for these claims can be found, e.g., in the specification at page 3, lines 18-25.New claim 48 is directed to a pharmaceutical composition comprising a peptide of the invention, as specified in claims 36, 37, 38, 40, 46 and 47. Support for this claim is found, e.g., in the specification at page 14, line 7, through page 18, line 8, specifically, at page 16, lines 3-7.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned agent at the Los Angeles, California telephone number (310) 789-5153 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Date: June 16, 2005

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